Glucose Tolerance and Insulin Resistance in the JCR:LA-Corpulent Rat: Effect of Miglitol (Bay m1099)

J.C. Russell, S.E. Graham, and P.J. Dolphin

A standardized meal tolerance test (MTT) using 5 g rat chow provides a sensitive index of insulin and glucose metabolism in the insulin-resistant, hyperinsulinemic, hypertriglyceridemic, and atherosclerosis-prone JCR:LA-corpulent (cp) strain of rats. The MTT revealed differences in insulin/glucose metabolism that were not evident in either an intravenous (IVGTT) or intraperitoneal (IPGTT) glucose tolerance test. The glycemic response of control rats to a 5-g carbohydrate test meal containing miglitol (Bay m1099) was sharply reduced, with a 50% effective dose (ED_{50}) of 36.4 ± 7.5 mg/100 g food. At a dose of 60 mg/100 g food, the plasma glucose curve was flat and indistinguishable from that found in the nonfed state. The plasma insulin response was similarly reduced, with an ED_{50} of 42.8 ± 14.8 mg/100 g food. Obese male rats were treated with miglitol at 60 mg/100 g food from 6 to 12 weeks of age. Treated rats had a significantly reduced food consumption and lower body weight at 12 weeks of age ($P < .05$). The treatment resulted in no significant changes in serum lipid concentrations. When subjected to the MTT using control (non–miglitol-containing) food, treated rats demonstrated markedly improved insulin sensitivity, with a greatly reduced insulin response, which may reflect an improved hepatic glucose metabolism. The results confirm that miglitol is highly effective in this obese insulin-resistant animal model. It reduced postprandial glycemic and insulin responses, and on long-term treatment, it improved glucose and insulin metabolism. These beneficial metabolic changes suggest that miglitol may have vascular protective effects in insulin-resistant states.

THE METABOLIC SYNDROME characterized by abdominal obesity, insulin resistance, and resultant hyperinsulinemia and hypertriglyceridemia is very common in prosperous societies. It is strongly associated with the development of atherosclerosis and symptomatic cardiovascular disease.[1,2] Insulin resistance is the central component of the syndrome rather than frank diabetes. Quantitative assessment of the insulin resistance is difficult, as the glucose tolerance may be relatively normal, albeit at the expense of marked hyperinsulinemia. The plasma insulin concentration provides an index of insulin resistance but is variable with the time of day and food intake, and in this very stress-sensitive strain, it is labile in response to stress. Studies on rats in our laboratory require the quantification of changes in insulin resistance. We have found both a conventional intravenous glucose tolerance test (IVGTT) and an intraperitoneal glucose tolerance test (IPGTT) to be insensitive and inadequate. A standardized meal tolerance test (MTT) provides much more sensitivity and is obtained under conditions close to those of the normal unmanipulated rat.

The JCR:LA-corpulent (cp) rat developed by Koletsky[3] and Hansen[4] is an animal model for the metabolic syndrome. If homozygous for the autosomal recessive *cp* gene, the rats (cp/cp) lack any leptin receptor[5] and are obese, insulin-resistant, hyperinsulinemic, and hypertriglyceridemic.[6-9] Male cp/cp rats spontaneously develop atherosclerosis that progresses to advanced lesions and leads to ischemic myocardial lesions.[10,11] Female cp/cp rats do not develop cardiovascular disease until an advanced age, and homozygous normal (+/+) lean rats are largely spared this disease. JCR:LA-cp rats strongly mimic the human population, with normal and resistant (+/+) animals, as well as cp/cp and disease-prone animals. We have shown that treatments that reduce the hyperinsulinemia also prevent the development of cardiovascular disease,[12-15] whereas a reduction of the hyperlipidemia, alone is not protective.[16] Treatment with the calcium channel antagonists nifedipine[17] and nisoldipine[18] is cardioprotective, probably by inhibiting vasospasm secondary to a defective endothelium-dependent relaxation factor.[19] Evidence to date suggests that endothelial damage due to hyperinsulinemia is a critical factor in the development of cardiovascular disease in this animal model.[20,21] The assessment of insulin sensitivity in these animals is essential for studies of the development of both the insulin resistance itself and potential pharmacological treatments.

Miglitol (Bay m1099) is an α-glucosidase inhibitor that is a deoxynojirimycin derivative,[22] and has been suggested to have no extraintestinal effects on glucose control.[23] We have studied the effects of miglitol on plasma glucose and insulin responses to a carbohydrate test meal in the male cp/cp rat of the JCR:LA-cp strain. Further, we have examined the effect of miglitol treatment from 6 to 12 weeks of age on both insulin sensitivity and plasma lipids. We report that miglitol is effective at low doses and has beneficial effects on postprandial glucose and insulin responses in this insulin-resistant animal model.

MATERIALS AND METHODS

Animals

Male rats of the JCR:LA-cp strain, obese (cp/cp) and lean (+/? or a 2:1 mixture of heterozygotes, cp/+, and homozygotes, +/+), were raised in our established breeding colony at the University of Alberta as previously described.[15] The rats for these studies were weaned at 3 weeks of age and housed initially in pairs in polycarbonate cages on woodchip bedding at 20°C and 55% relative humidity. The lighting was on a 12-hour cycle, with either normal lights on at 6 AM and off at 6 PM or the reverse to allow study and testing during the dark phase of the diurnal cycle when the animals are active. At 6 weeks of age, the rats were housed separately.

Food was available at all times (Teklad Rodent Diet; Harlan

From the Department of Surgery, University of Alberta, Edmonton, Alberta; and Department of Biochemistry, Dalhousie University, Halifax, Nova Scotia, Canada.

Submitted March 6, 1998; accepted December 28, 1998.

Supported by Bayer, the Medical Research Council of Canada, and the Heart and Stroke Foundation of Nova Scotia.

Address reprint requests to J.C. Russell, PhD, Department of Surgery, 275 Heritage Medical Research Centre, University of Alberta, Edmonton, Alberta T6G 2S2, Canada.

0026-0495/99/4806-0006$10.00/0

Sprague-Dawley, Madison, WI). This is a corn and wheat–based diet of less than 4% total lipid[24] and 23% protein content; the energy content is approximately 3.3 kcal/g. For treatment purposes, miglitol was incorporated into powdered diet that was then moistened, pelleted by extrusion through a die, and air-dried. Test meals consisted of 5 g chow-like synthetic diet (D11721; Research Diets, New Brunswick, NJ) incorporating miglitol at various doses.

All animal care and experimental procedures were in conformity with the guidelines of the Canadian Council on Animal Care and were subject to institutional review and approval.

Experimental Protocols

Animals used for the glucose tolerance tests were maintained on normal rat chow without any treatment until the tests. A separate group of rats were fed chow containing miglitol at various dosages from 6 to 12 weeks of age. All rats were killed under halothane anesthesia by bleeding from the heart. Serum for lipid analysis was separated and frozen at −70°C until analyzed.

IVGTT

The IVGTT procedure was performed on 12-week-old rats during the light phase following an overnight period of food deprivation. The animals were anesthetized with 3% to 4% halothane in oxygen and maintained on 2% halothane on a warmed table. A carotid artery was cannulated with PE50 polyethylene tubing (Intramedic; Becton Dickinson, Parsippany, NY) filled with heparinized saline. D-Glucose 0.5 g/kg body weight was injected into the contralateral jugular vein using a 27-gauge needle. Blood was sampled from the carotid cannula before and at fixed times after the glucose load, and the plasma was separated for analysis of glucose and insulin.

MTT

The insulin and glucose metabolism of the cp/cp rat is abnormally responsive to stress or disturbance. To reduce variability, glucose tolerance tests were performed on conscious rats under a specific protocol and during the dark (active) phase of the diurnal cycle. At 9 weeks of age, the rats were acclimatized to an isolated room with lights on a reversed cycle (off at 6 AM and on at 6 PM). At 10 weeks of age, the rats were conditioned to a sham procedure with removal of food for 24 hours, presentation of a control test meal, and a mock tail bleed. The animals were studied weekly between 11 and 13 weeks of age, with three only blood samples taken during each session. They were subjected to a different schedule of sampling times during each session so as to obtain two samples from each rat at each of six time points without an excessive amount of blood taken.

Animals were warmed on a heated table to ensure vasodilation of the tail, and 0.5 mL blood was taken from the tip of the tail. The rats were then replaced in their cage, with the test meal given at 9 AM (3 hours into the dark phase). Timing was started when 50% of the test meal was consumed, and blood samples were taken at 30, 60, 90, 180, and 240 minutes for analysis of glucose and insulin. All rats ate the full test meal within 15 minutes of presentation.

IPGTT

An intraperitoneal glucose injection was used to provide a rapid glucose challenge with minimal stress and without the possible confounding effects of anesthesia or indwelling cannulae. A D-glucose (50% wt/vol) solution was injected intraperitoneally using a 27-gauge needle and a dose of 1 g/kg body weight for lean +/? rats. The cp/cp rats were injected with a glucose load equivalent to the mean mass of glucose administered to +/? rats, thus essentially normalizing the dose to the lean body mass of the rat. IPGTTs were performed in the same manner as the MTT, with the exception that no food was given and blood samples were taken at time 0 (before glucose injection) and at 15, 30, 60, 90, and 120 minutes.

Analytical Methods

The plasma glucose level was measured using a rapid glucose oxidase technique (Beckman Instruments, Brea, CA). Insulin was assayed with a double-antibody radioimmunoassay technique (Kabi Pharmacia, Uppsala, Sweden) and rat insulin standards. Serum lipid concentrations were determined by the gas chromatographic total lipid profile technique of Kuksis et al.[25]

Statistical Analyses

The area under the curve (AUC) for the plasma glucose response to the test meal was calculated from the data at 30, 60, and 90 minutes following the meal challenge. Mean plasma levels for rats in the no-food control condition were subtracted from the values for individual rats, and the results were summed rat by rat to effectively yield the AUC over the period of 15 to 105 minutes. Units are expressed as millimoles per minute. Curve-fitting was performed with the Sigmaplot program (SPSS, Chicago, IL). Dose-response data for the effect of miglitol were analyzed using the program ALLFIT.[26] This program fits the entire data set to the logistic equation and performs statistical comparisons between groups. Other data were analyzed by ANOVA and differences were tested by Bonferroni's method, with a P level less than .05 indicating significance. Data are presented as the mean ± SEM.

RESULTS

IVGTT

Glucose and insulin responses to the IVGTT of both +/? and cp/cp rats are shown in Fig 1. The plasma glucose response to the 0.5-g/kg load is greater in cp/cp rats, which received 37%

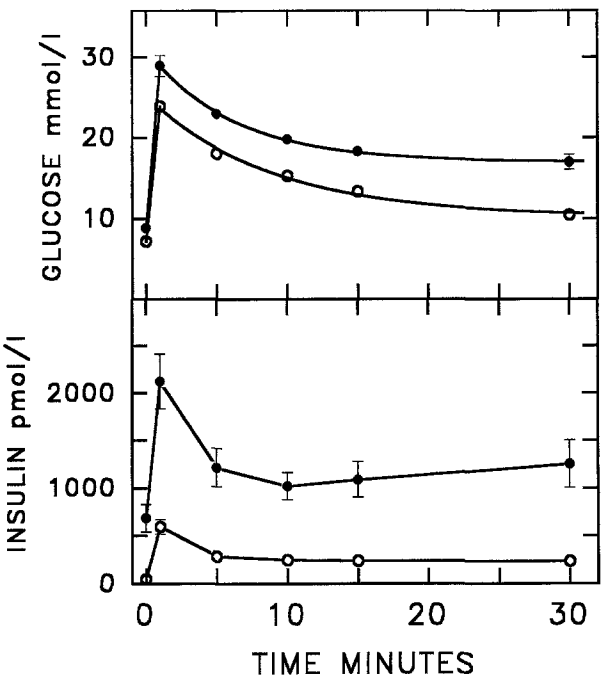

Fig 1. Plasma glucose and insulin in response to an intravenous glucose bolus of 0.5 g/kg body weight at time 0. Data are the mean ± SEM for 6 rats at 12 weeks of age in each group. ○, +/? rats; ●, cp/cp rats. Asymptotic glucose values were significantly greater in cp/cp rats ($P < .001$).

more glucose due to their greater body weight. The principal difference in the response is the failure of plasma glucose in the cp/cp rat to return to the fasting range of approximately 10 mmol/L, as in +/? rats. A simple analysis based on a simple exponential decay (glucose, $g = g_0e^{-kt}$) yields a value for k, the rate constant, of 0.214 ± 0.023 and 0.111 ± 0.017 min^{-1} for +/? and cp/cp rats, respectively ($P < .01$). However, this analysis is misleading, as it assumes an ultimate concentration of 0. A more appropriate measure of the initial rate constant for glucose clearance is obtained by fitting the data to the equation, $g = g' + g_0e^{-kt}$, which yields k values of 0.113 ± 0.08 and 0.166 ± 0.030 min^{-1} for +/? and cp/cp rats, respectively (NS, $P > .1$). However, the values for g', the asymptotic glucose concentration, were 10.2 ± 0.27 and 16.9 ± 0.34 mmol/L for +/? and cp/cp rats, respectively, and this difference was highly significant ($P < .001$). The plasma insulin response to the glucose load was much greater in cp/cp rats and insulin levels remained elevated at 30 minutes ($P < .001$).

IPGTT

Fasting glucose levels were not different in +/+ and cp/cp rats subjected to the IPGTT. The glucose challenge resulted in a modest increase in glucose that was not different between +/? and cp/cp animals and was followed by a return to fasting concentrations by 60 minutes. Fasting insulin levels were 14-fold higher in cp/cp rats versus +/? rats. In response to the intraperitoneal glucose challenge, insulin in +/? rats increased from 100 to 250 pmol/L, decreasing to baseline levels by 45 minutes. In contrast, cp/cp rats showed a modest biphasic increase from 1,500 pmol/L, with an initial peak of 2,200 pmol/L and a return to baseline by 60 minutes (Fig 2).

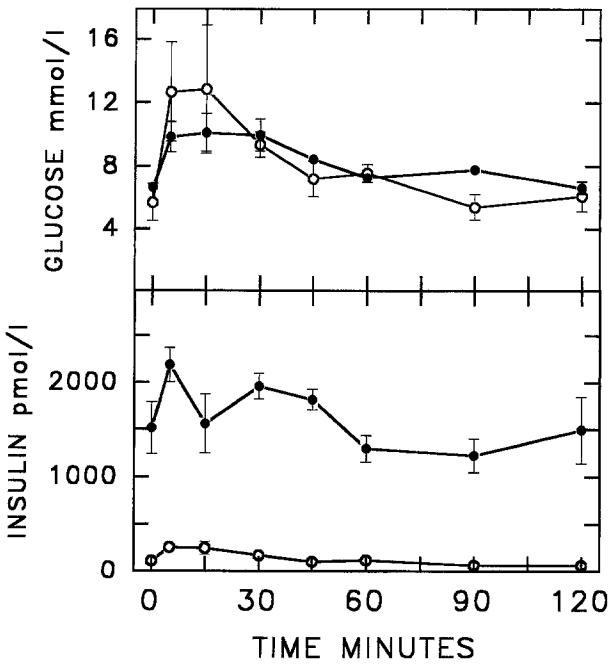

Fig 2. Plasma glucose and insulin in response to an intraperitoneal glucose bolus of 1.0 g/kg body weight in +/? rats at time 0. Data are the mean ± SEM for 6 rats at 12 weeks of age in each group. ○, +/? rats; ●, cp/cp rats.

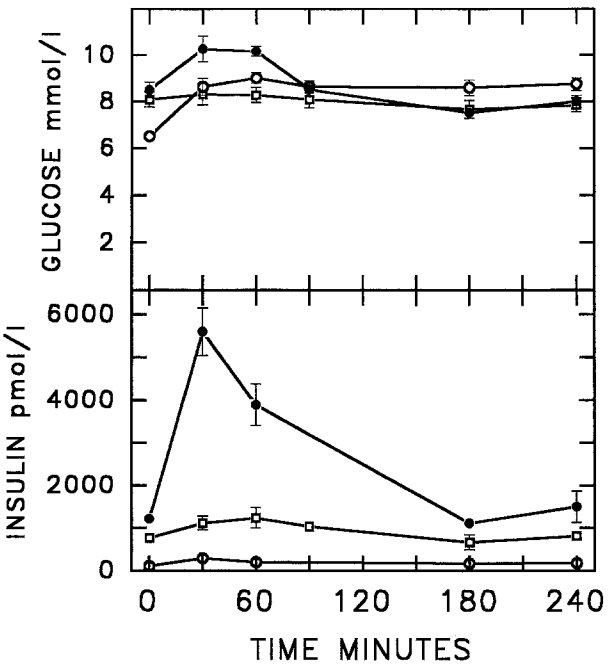

Fig 3. Plasma glucose and insulin in response to a 5-g test meal. Data are the mean ± SEM for 6 rats at 12 weeks of age in each group. ○, +/? rats; ●, cp/cp rats; □, cp/cp rats given no food.

MTT

Fasting plasma glucose concentrations were slightly higher in cp/cp rats versus +/? rats in this study ($P < .001$), but were not in a hyperglycemic range and remained stable in the absence of food. Both genotypes showed a modest increase in glucose of about 2 mmol/L in response to treatment, with glucose in cp/cp rats returning to 8 mmol/L by 90 minutes, when there was no longer any significant difference between +/? and cp/cp rats ($P > .05$). The cp/cp rats were hyperinsulinemic (~1,000 pmol/L) in the fasting state, and insulin concentrations were higher than 5,000 pmol/L in response to the test meal. There was no response of insulin or glucose to the handling and sampling of the rats, as shown by the nonfed group (Fig 3).

Effects of Miglitol

The incorporation of miglitol 60 mg/100 g into the test meal of untreated rats resulted in complete abolition of the insulin response (Fig 4). This was accompanied by a delay and blunting of the modest increase in plasma glucose in cp/cp control rats ($P < .0001$ at 30 and 60 minutes). Rats that were provided from 6 weeks of age with food containing miglitol 60 mg/100 g were tested with control food. These rats had markedly greater insulin sensitivity, with a greatly decreased insulin response at 30 minutes ($P < .002$) and a reduced glucose increase. Similar studies were performed on untreated cp/cp rats with test meals containing a range of miglitol concentrations up to 90 mg/100 g. The AUC for glucose was a strong function of the miglitol dose, reducing to 0 with a 50% effective dose (ED_{50}) of 36.4 ± 7.6 mg/100 g. The peak insulin response (at 30 minutes) showed the same pattern, with an ED_{50} of 42.8 ± 14.8 mg/100 g (Fig 5).

Plasma lipid values were not significantly changed by the 6-week treatment with miglitol 60 mg/100 g in the food (Table

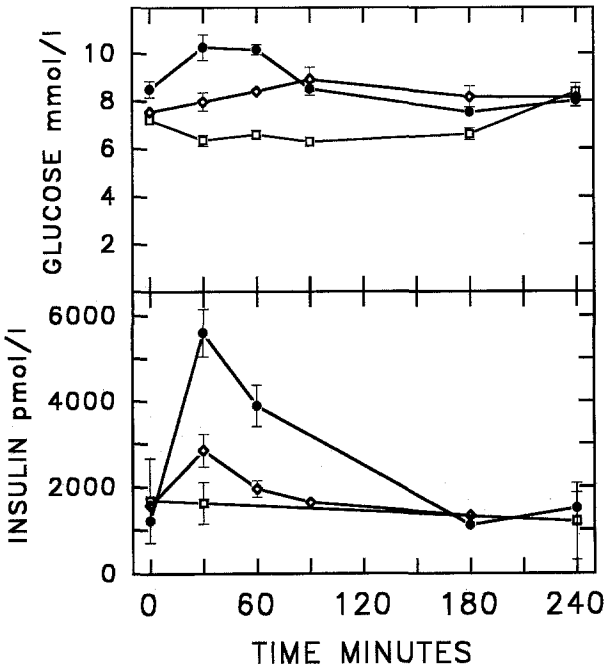

Fig 4. Plasma glucose and insulin in response to a 5-g test meal. Data are the mean ± SEM for 6 rats at 12 weeks of age in each group. ●, cp/cp control; □, cp/cp rats given food containing miglitol 60 mg/100 g; ◇, rats treated for 6 weeks with miglitol 60 mg/100 g food and given a test meal of control food containing no miglitol. Plasma glucose was significantly lower in miglitol-treated versus control rats at 30 and 60 minutes ($P < .0001$). The plasma insulin response was also lower at 30 minutes ($P < .002$).

1). There were small but significant ($P < .05$) decreases in both food intake and body weight (10% and 8%, respectively) in miglitol-treated cp/cp rats (Table 2).

DISCUSSION

The cp/cp rat at 12 weeks of age does not show any significant fasting hyperglycemia (Fig 1). However, this quasi-normal control of plasma glucose is achieved at the expense of marked fasting hyperinsulinemia. With administration of an intravenous glucose challenge, cp/cp rats are able to mount an effective initial decrease in glucose that is as good as or better than that of +/+ rats. However, this is achieved only with an even greater (threefold) hyperinsulinemic response, and unlike the case with +/? rats, plasma glucose reached a plateau at 30 minutes that was significantly elevated compared with the fasting condition. Thus, the impairment in the cp/cp rat is not simply in the rate of glucose clearance, but involves other regulatory factors including the insulin clearance rate and hepatic glucose metabolism.[7]

The IVGTT is a very strong challenge to insulin/glucose metabolism and is a poor indicator of normal function, as the enteroinsular axis is not involved. The practical necessity to perform the IVGTT under anesthesia introduces the additional variable of the anesthetic agent. This is of potential concern, notwithstanding evidence that halothane induces a basal state of insulin/glucose metabolism.[27] The alternative approach is surgical implantation of indwelling venous cannulae that are exteriorized to allow intravenous glucose injection and blood sampling from the conscious rat. Such a procedure requires anesthesia either on the day of study or several days earlier. In either case, the surgery, anesthesia, and maintenance of the cannulae cause significant stress in the animals that we have shown to be highly stress-sensitive.[28,29] The IPGTT does not require anesthesia in the rat, results in rapid absorption of glucose, and was used for comparison to the IVGTT in anesthetized animals. The plasma glucose response was much more moderate in both genotypes, with a peak at 5 minutes, reflecting the slower transfer of glucose to the circulation. The reduced insulin response in +/? rats probably is a result of the lower peak glucose levels. The cp/cp rats had twofold higher fasting plasma insulin levels than anesthetized IVGTT animals, possibly due to their awake state, but only a small further increase. Overall, rats under the IPGTT protocol were physiologically more normal but showed a markedly attenuated insulin response to the glucose challenge.

The MTT (Fig 3) provides a clear-cut index of insulin function, with only a modest glycemic response in either genotype but a dramatically greater insulin response in the cp/cp rat. The differentiation between normally insulin-sensitive +/? rats and insulin-resistant cp/cp rats is greater versus the IVGTT or IPGTT. This may reflect the essentially normal metabolic state of the rats, handled in a familiar manner and eating at the same time of day as the initial "meal" in the dark cycle. The extreme insulin response is consistent with our previous report of massive hypersecretion of insulin from the isolated pancreas of the cp/cp rat in response to gastric

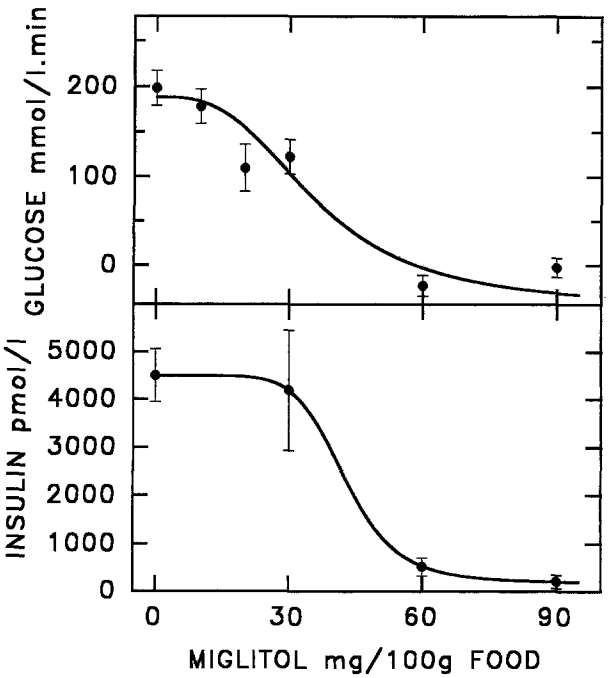

Fig 5. Dose-response curves to miglitol in the test meal for glucose and insulin. (A) Plasma glucose AUC in mmol/L · min; (B) comparable data for peak plasma insulin level (at 30 minutes). Values are the mean ± SEM for 6 rats at 12 weeks of age in each group. The ED_{50} for miglitol is 36.4 ± 2.5 for the glucose response and 42.8 ± 14.8 for the insulin response.

Table 1. Whole Serum Lipid Concentrations in Miglitol-Treated JCR:LA-cp Rats

Group	No. of Rats	Cholesterol	Cholesteryl Esters	Phospholipids	Triglycerides	Total Cholesterol
+/? control	6	0.34 ± 0.01	1.00 ± 0.04	0.83 ± 0.02	0.33 ± 0.03	1.34 ± 0.04
cp/cp control	6	0.66 ± 0.05	1.95 ± 0.10	2.47 ± 0.23	3.94 ± 1.06	2.62 ± 0.15
cp/cp miglitol-treated	6	0.67 ± 0.02	1.74 ± 0.04	2.35 ± 0.11	3.12 ± 0.46	2.41 ± 0.07

NOTE. Values are the mean ± SEM in mmol/L. The dose of miglitol was 60 mg/100 g food. Lipid concentrations are significantly lower in +/? rats *v* either cp/cp group ($P < .01$), but there was no significant difference between miglitol-treated and control cp/cp rats.

inhibitory polypeptide and arginine.[30] The greater insulin response of the cp/cp rat versus the fa/fa Zucker rat[30] appears to be due to the absence of the leptin receptor in cp/cp rats and a consequent absence of leptin inhibition of insulin release.[31,32]

The addition of miglitol 60 mg/100 g to the food used in the MTT was effective in abolishing both the glycemic and hyperinsulinemic responses to the meal challenge (Fig 4). The ED_{50} for miglitol is 43 and 36 mg/100 g for insulin and glucose responses, respectively—a very consistent result (Fig 5). Animals treated with miglitol for 6 weeks remained hyperinsulinemic (1,560 ± 101 *v* 95 ± 6 pmol/L for +/? rats; Fig 3) in the fasting state and thus insulin-resistant, as shown by the time 0 values in Fig 4. However, when fed a test meal without miglitol, these rats showed greatly reduced glucose and insulin responses that were highly significant. This effect may be due to some retained miglitol within the circulation; however, the agent has effects in the lumen of the gut and is rapidly excreted from the plasma, with a half-life of about 1 hour.[33] Thus, the reduction found in the glycemic and insulin responses appears to reflect a real improvement in insulin sensitivity. The modest decreases in food intake and body weight (Table 2) are consistent with such a change but, on the basis of other studies in this strain, are far too small to account for the reduction in insulin resistance.[34] The improvement in metabolic status did not extend to a reduction in plasma lipid levels (Table 1). Since the hypertriglyceridemia precedes and may play a role in the induction of insulin resistance in peripheral tissues,[35] improvements in lipid metabolism would not necessarily be expected. The improvement similarly did not result in a reduction in elevated fasting insulin, and thus may be a reflection of enhanced hepatic glucose uptake in response to a reduced peak glycemic load over a period of time. Identification of the underlying mechanism will depend on successful elucidation of the unknown dysfunction(s) of insulin signal transduction in insulin resistance. The persistence of fasting hyperinsulinemia in miglitol-treated rats may reflect the absence of an important leptin-mediated regulation of pancreatic insulin release in the cp/cp rat.[5,31]

Table 2. Effect of Miglitol on Food Intake and Body Weight of JCR:LA-cp Rats at 11 to 13 Weeks of Age

Group	No. of Rats	Food Intake (g/d)	Body Weight (g)
+/? control	6	21.7 ± 1.0	296 ± 6
cp/cp control	6	36.6 ± 0.60	468 ± 7.4
cp/cp miglitol-treated	6	32.6 ± 1.39*	433 ± 13*

NOTE. Values are the mean ± SEM. Miglitol was incorporated into the feed at 60 mg/100 g. Values are significantly less for +/? control rats *v* cp/cp rats either treated or untreated.

*$P < .05$ *v* cp/cp control.

Tulp et al[36] and DeBuono et al[37] have also reported evidence of modest metabolic improvement in other strains of obese rats with miglitol treatment. Bollen et al[38] have found a reduction in hepatic glycogenolysis in the presence of miglitol. Thus, it appears that in both humans and obese rats, miglitol reduces both the postprandial glycemic response and the concomitant insulin release.

We have previously shown that the nonabsorbed α-glucosidase inhibitor acarbose reduces hyperinsulinemia and is cardioprotective in the cp/cp male rat.[39] The MTT provided a sensitive and reproducible assessment of the effects of agents, such as acarbose and miglitol. The results provide clear evidence of the highly effective response to both acute and chronic treatment with miglitol in the insulin-resistant cp/cp rat. Such amelioration of the hyperglycemia and especially the extreme postprandial peak hyperinsulinemia in the cp/cp rat should result in both antiatherosclerotic and cardioprotective effects, as found with other agents.[12,15,36] The cp/cp rat is a very close analog of the obese insulin-resistant human, and similar protective effects may be found in humans even in the presence of continuing insulin resistance.

ACKNOWLEDGMENT

Juno Brady, Bruce Stewart, and Eva Dolinsky provided invaluable technical assistance.

REFERENCES

1. Després J-P, Moorjani S, Lupien PJ, et al: Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. Arteriosclerosis 10:497-511, 1990

2. Steiner G: Hyperinsulinemia and hypertriglyceridemia. J Intern Med 736:23-26, 1994 (suppl)

3. Koletsky S: Pathologic findings and laboratory data in a new strain of obese hypertensive rats. Am J Pathol 80:129-142, 1975

4. Greenhouse DD, Michaelis OE, Peterson RG: The development of fatty and corpulent rat strains, in Hansen CT, Michaelis OE (eds): New Models of Genetically Obese Rats for Studies in Diabetes, Heart Disease, and Complications of Obesity. Bethesda, MD, National Institutes of Health, 1988, pp 3-6

5. Wu-Peng XS, Chua SC Jr, Okada N, et al: Phenotype of the obese Koletsky (*f*) rat due to Tyr763 stop mutation in the extracellular domain of the leptin receptor (Lepr). Diabetes 46:513-518, 1997

6. Russell JC, Ahuja SK, Manickavel V, et al: Insulin resistance and impaired glucose tolerance in the atherosclerosis prone LA/N-corpulent rat. Arteriosclerosis 7:620-626, 1987

7. Russell JC, Graham S, Hameed M: Abnormal insulin and glucose metabolism in the JCR:LA-corpulent rat. Metabolism 43:538-543, 1994

8. Russell JC, Koeslag DG, Amy RM, et al: Plasma lipid secretion and clearance in hyperlipidemic JCR:LA-corpulent rats. Arteriosclerosis 9:869-876, 1989

9. Vance J, Russell JC: Hypersecretion of VLDL, but not HDL, by hepatocytes from the JCR:LA-corpulent rat. J Lipid Res 31:1491-1501, 1990

10. Russell JC, Amy RM: Myocardial and vascular lesions in the LA/N-corpulent rat. Can J Physiol Pharmacol 64:1272-1280, 1986

11. Russell JC: The atherosclerosis-prone JCR:LA-corpulent rat, in Woodford FP, Davignon J, Sniderman A (eds): Atherosclerosis X: Proceedings of the 10th International Symposium on Atherosclerosis. Amsterdam, The Netherlands, Elsevier, 1995, pp 121-125

12. Russell JC, Amy RM, Manickavel V, et al: Effects of chronic ethanol consumption in atherosclerosis-prone JCR:LA-corpulent rat. Arteriosclerosis 9:122-128, 1989

13. Russell JC, Amy RM, Manickavel V, et al: Prevention of myocardial disease in JCR:LA-corpulent rats by running. J Appl Physiol 66:1649-1655, 1989

14. Russell JC, Dolphin PJ, Graham SE, et al: Improvement of insulin sensitivity and cardiovascular outcomes in the JCR:LA-cp rat by D-fenfluramine. Diabetologia 41:380-389, 1998

15. Russell JC, Amy RM, Graham SE, et al: Inhibition of atherosclerosis and myocardial lesions in the JCR:LA-cp rat by β,β′-tetramethylhexadecanedioic acid (MEDICA 16). Arterioscler Thromb Vasc Biol 15:918-923, 1995

16. Russell JC, Amy RM, Koeslag DG, et al: Independence of myocardial disease in the JCR:LA-corpulent rat of plasma cholesterol concentration. Clin Invest Med 14:288-295, 1991

17. Russell JC, Koeslag DG, Dolphin PJ, et al: Prevention of myocardial lesions in JCR:LA-corpulent rats by nifedipine. Arteriosclerosis 10:658-664, 1990

18. Russell JC, Dolphin PJ, Graham SE, et al: Cardioprotective and hypolipidemic effects of nisoldipine in the JCR:LA-cp rat. J Cardiovasc Pharmacol 29:586-592, 1997

19. O'Brien SF, McKendrick JD, Radomski MW, et al: Vascular wall reactivity in conductance and resistance arteries: Differential effects of insulin resistance. Can J Physiol Pharmacol 76:72-76, 1998

20. Richardson M, Schmidt AM, Graham SE, et al: Vasculopathy and insulin resistance in the JCR:LA-cp rat. Atherosclerosis 138:135-146, 1998

21. O'Brien SF, Russell JC: Insulin resistance and vascular wall function: Lessons from animal models. Endocrinol Metab 4:155-162, 1997 (review)

22. Katsilambros N, Philippides P, Toskas A, et al: A double-blind study on the efficacy and tolerance of a new alpha-glucosidase inhibitor in type-2 diabetics. Arzneimittelforschung 36:1136-1138, 1986

23. Sels JP, Nauta JJ, Menheere PP, et al: Miglitol (Bay m 1099) has no extraintestinal effects on glucose control in healthy volunteers. Br J Clin Pharmacol 42:503-506, 1996

24. Russell JC, Amy RM, Dolphin PJ: Effect of dietary n-3 fatty acids on atherosclerosis prone JCR:LA-corpulent rats. Exp Mol Pathol 55:285-293, 1991

25. Kuksis A, Myher JJ, Geher K, et al: Comparative determination of plasma cholesterol and triacylglycerol levels by automated gas-liquid chromatographic and autoanalyzer techniques. J Chromatogr 146:393-412, 1978

26. De Lean A, Munson PJ, Rodbard D: Simultaneous analysis of families of sigmoidal curves: Application to bioassay, radioligand assay, and physiological dose-response curves. Am J Physiol 235:E97-E102, 1978

27. Heath DF, Frayne KN, Rose JG: Rates of glucose utilization and glucogenesis in rats in the basal state induced by halothane anesthesia. Biochem J 162:643-651, 1977

28. Leza JC, Salas E, Sawicki G, et al: The effect of stress on homeostasis in JCR:LA-cp rats. Role of nitric oxide. J Pharmacol Exp Ther 28:1397-1403, 1998

29. McArthur MD, Graham SE, Russell JC, et al: Exaggerated stress-induced release of non-esterified fatty acids in JCR:LA-corpulent rats. Metabolism 47:1383-1390, 1998

30. Pederson RA, Campos RV, Buchan AMJ, et al: Comparison of the enteroinsular axis in two strains of obese rats: The fatty Zucker and JCR:LA-corpulent. Int J Obes 15:461-470, 1991

31. Emilsson V, Lim YL, Cawthorne MA, et al: Expression of the functional leptin receptor in RNA in pancreatic islets and directly inhibitory action of leptin on insulin secretion. Diabetes 46:313-316, 1997

32. Chua SC Jr, White DW, Wu-Peng XS, et al: Phenotype of fatty due to Gln269Pro mutation in the leptin receptor (Lepr). Diabetes 45:1141-1143, 1996

33. Ahr HJ, Boberg M, Brendel E, et al: Pharmacokinetics of miglitol. Absorption, distribution, metabolism, and excretion following administration to rats, dogs, and man. Arzneimittelforschung 47:734-745, 1997

34. Russell JC, Graham SE, Dolphin PJ, et al: Effects of benfluorex on serum triacylglycerols and insulin sensitivity in the corpulent rat. Can J Physiol Pharmacol 74:879-886, 1996

35. Russell JC, Bar-Tana J, Shillabeer G, et al: Development of insulin resistance in the JCR:LA-cp rat: Role of triacylglycerols and effects of MEDICA 16. Diabetes 47:770-778, 1998

36. Tulp OL, Szepesi B, Michaelis OE IV, et al: The effects of low-dose Bay-M-1099 (miglitol) on serum lipids and liver enzyme activity of obese and obese-diabetic corpulent rats. Comp Biochem Physiol 99:241-246, 1991

37. DeBuono JF, Michaelis OE IV, Tulp OL: The effects of intestinal glucosidase in inhibitory Bay M1099 (miglitol) on glycemic status of obese-diabetic rats. Gen Pharmacol 24:504-515, 1993

38. Bollen M, Vandebroeck A, Stalmans W: 1-Deoxynojirimycin and related compounds inhibit glycogenolysis in the liver without affecting the concentration of phosphorylase a. Biochem Pharmacol 37:905-909, 1988

39. Russell JC, Koeslag DG, Dolphin PJ, et al: Beneficial effects of acarbose in the atherosclerosis-prone JCR:LA-corpulent rat. Metabolism 42:218-223, 1993